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(54) **THERAPEUTIC SWABS FOR TREATING
UPPER RESPIRATORY INFECTIONS**

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(57) **ABSTRACT**

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Compounds and methods for preventing or treating upper respiratory virus infections in humans and animal species are disclosed. The compounds may exhibit antimicrobial, antiviral, anti-inflammatory, anticoagulant or cytoprotective activities. The methods may deliver compounds to be delivered to the nasal and oral cavities, nasopharynx, and posterior pharynx, the primary sites of upper respiratory infections, such as influenza, SARS, and SARS-CoV-2. Therapeutic swabs comprising one or more compounds are may be used to deliver one or more compounds to deliver the above primary sites of the individuals infected with one or more upper respiratory viruses or other pathogens.

Therapeutic Swabs for Treating Upper Respiratory Infections

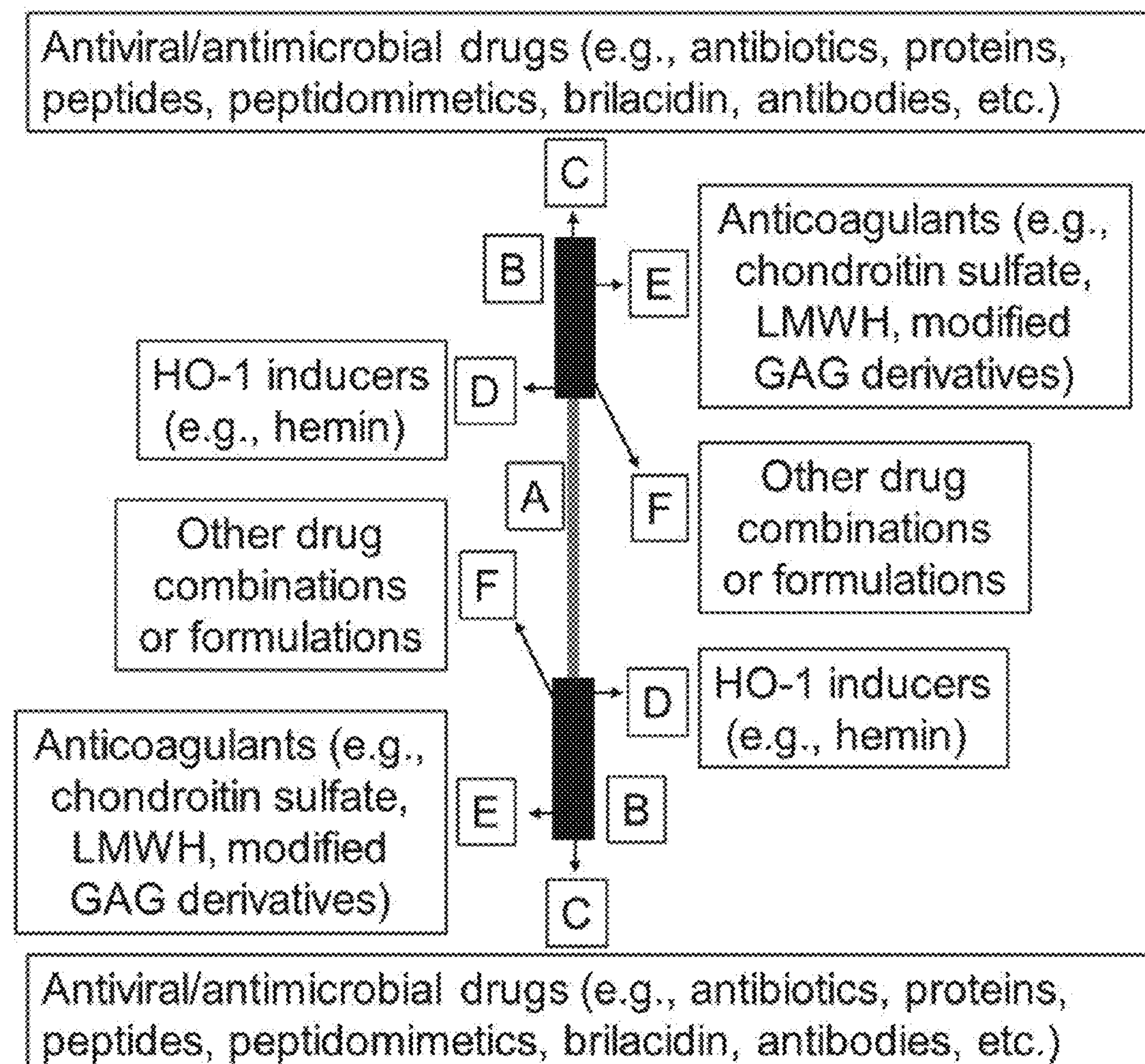


Figure 1

Therapeutic Swabs for Treating Upper Respiratory Infections

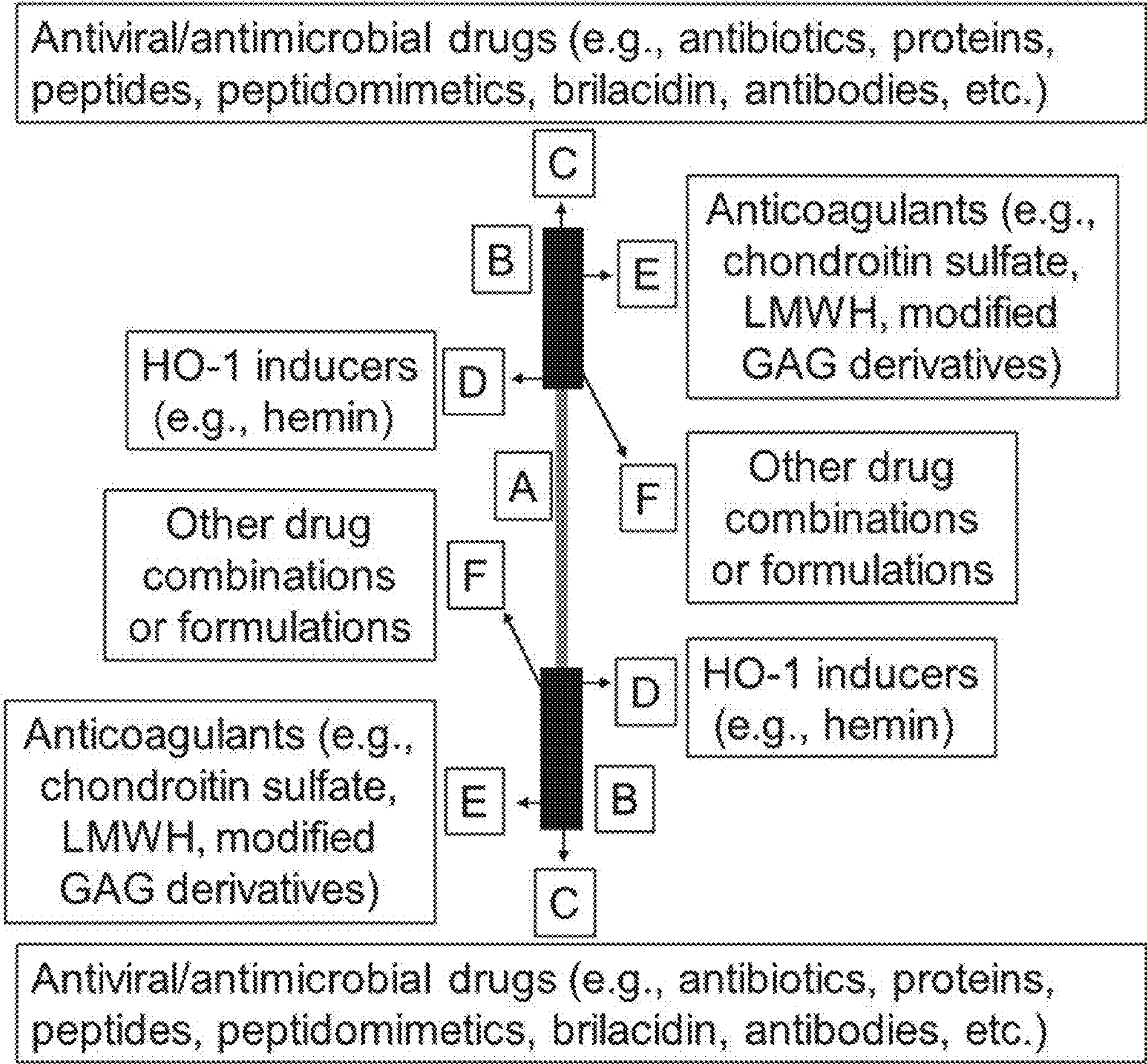
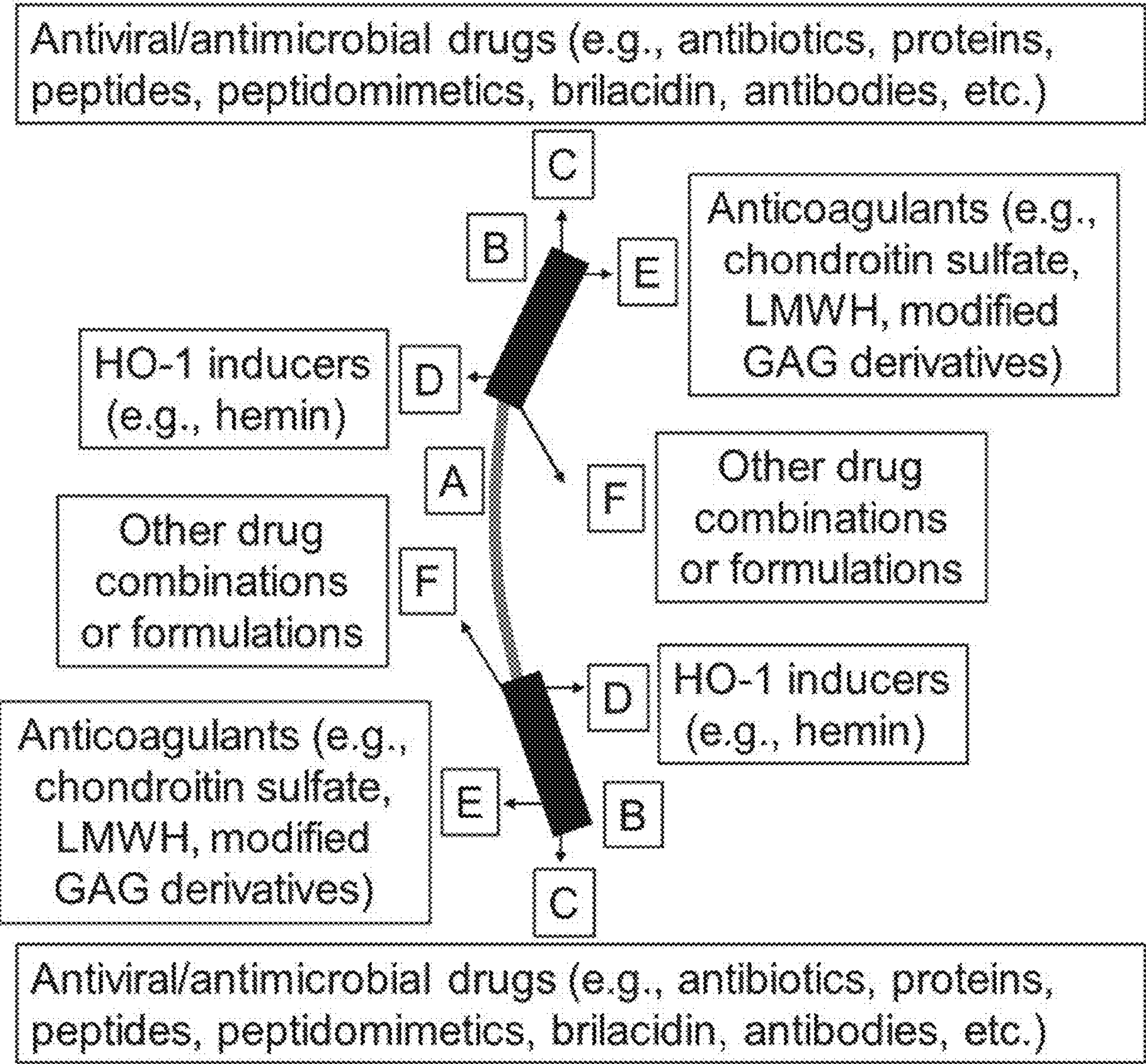


Figure 2

Therapeutic Swabs for Treating Upper Respiratory Infections



THERAPEUTIC SWABS FOR TREATING UPPER RESPIRATORY INFECTIONS

BACKGROUND OF THE INVENTION

[0001] Infections caused by upper respiratory pathogens, including the most dangerous novel class of COVID-19-causing coronavirus SARS-CoV-2 and its mutant variant strains, transmissible in close proximity, triggering respiratory illnesses and serious health complications, are responsible for a large number of hospitalizations and deaths every year and present a significant threat to the human health (Satia, et al. PLOS ONE. 15: e 0228544 (2020); Lai et al. Int. J. Antimicrob. Agents. 55:10593 (2020); Nakamichi et al. Scientific Reports. 11:4802 (2021). As of Aug. 30, 2021, according to the World Health Organization, COVID-19 has affected nearly 216 million individuals worldwide claiming more than 4.5 million lives with 38.5 million infections and in excess of 631,000 deaths in the United States (World Health Organization Dashboard: Aug. 30, 2021). These numbers are increasing daily at an alarming rate.

[0002] Rapid mutational changes in SARS-CoV-2 resulting in new highly contagious and more deadly variants have worsened the pandemic, posing difficult challenges to effective treatment (Volz et al. Cell. 184:64-75 (2021); Korber et al. Cell. 184:64-75 (2021); Davies et al. Science. 372: eabg3055 (2021)). Although vaccines are reportedly effective in reducing the severity of COVID-19 illnesses, hospitalizations, and deaths, none is yet known to prevent infections or reinfections of the vaccinated individuals by rapidly emerging highly contagious and more deadly mutant viral variants. In addition, children, older population, and individuals with underlying health conditions, all are at a significantly higher risk of acquiring the infection and developing hyperinflammatory syndrome and other severe health complications (Toniaty et al. Autoimmun. Rev. 19:102568 (2020); Gustine, J. N. & Jones, D. Am. J. Pathol. 191:4-17 (2021); Nikolich-Zugich et al. GeroScience. 342: 505-514 (2020); CDC, August 2021)). Therapeutic options for treating COVID-19 patients are limited and require hospitalizations.

[0003] The dire COVID-19 pandemic situation calls for an urgent need for safe and effective therapeutics along with convenient, preferably self-administering approaches, to treat the infected individuals at the early symptomatic stage of infection. It is critical for our own safety and also for minimizing the spread of the disease to others.

Highlights of the Invention

[0004] The present invention offers the first multifactorial therapeutic approach designed for specific and direct targeting the sites of upper respiratory infections.

[0005] The Therapeutic Swabs offers an innovative therapeutic device system designed to: (a) accommodate a plurality of unique combination of drugs exhibiting antiviral activity, antimicrobial activity, and other crucial innate host protective functions; and (b) deliver them simultaneously and specifically to the nasal cavity, nasopharynx, and posterior pharynx, the primary sites of upper respiratory infections.

[0006] This invention presents the first configuration design consisting of plurality of drugs possessing distinct functions, such as: (a) antiviral and antimicrobial activities to disrupt the pathogens and inhibit their

replication; (b) induce strong innate cytoprotective response to prevent virus-induced cell death; (c) anti-inflammatory activity to reduce inflammation associated with upper respiratory infections; and (d) partial anticoagulant activity to reduce the possibility of blood clotting reported in COVID-19 patients—all to collectively combat infections and provide an effective host protection.

[0007] The therapeutic approach presented in this invention is pivotal for our first defense against upper respiratory infections. It has a tremendous potential for its utility on a mass-scale to help control the currently out-of-control COVID-19 pandemic situation, and also as a safeguard for future viral outbreaks.

SUMMARY OF THE INVENTION

[0008] This invention addresses the critical and unmet needs related to upper respiratory infections—one of which is caused by the most prevalent, highly contagious, and deadly novel coronavirus SARS-CoV-2. It is of enormous global public health concern. Accordingly, the present invention relates to the first one-of-its-kind therapeutic approach consisting of multifunctional drugs intended for their direct delivery to the nasal cavity, nasopharynx, and posterior pharynx, the primary sites of upper respiratory infection, by means of drug-adsorbed or drug-conjugated Therapeutic Swabs device system. Since epithelial cells are the primary initial target site of upper respiratory infections, delivery of the drugs exhibiting various crucial biological functions directly to the sites of infection, presents this invention as a novel multifactorial therapeutic approach. This invention offers a convenient, efficient, specific and rapid drug application on a mass-scale presenting Therapeutic Swabs device system as an ideal therapeutic modality to treat the infected individuals and to effectively control the current out-of-control deadly COVID-19 pandemic and other respiratory infections.

BRIEF DESCRIPTION OF THE FIGURES

[0009] FIG. 1 illustrating the configuration of the therapeutic swabs device system comprising unique selection of drugs exhibiting crucial multiple functions depicted as [C], [D], [E] and [F] mounted on a straight stem.

[0010] FIG. 2 illustrating the configuration of the therapeutic swabs device system comprising unique selection of drugs exhibiting crucial multiple functions depicted as [C], [D], [E] and [F] mounted on a curved or flexible stem.

Wherein:

[0011] [A] is stem made from materials meeting requirements for general safety, preferably using biodegradable materials. The curved or flexible stem shown in FIG. 2 is designed for easy access to the nasal and oral cavities in the humans and in animals;

[0012] [B] represents drug-adsorbed or drug-conjugated swabs attached on both ends of the stem [A]. If desired, only one swab on the stem of the Therapeutic Swabs may be used;

[0013] The dimensional specifications (e.g., size, appearance, material density, and physical or chemical composition) for “stem” [A] and “swabs” [B] used in the Therapeutic Swabs device system are not explicitly defined; rather, these

are to be designed for drug delivery in the humans and in animals based on the anatomy of their nasal and oral cavities;

[0014] The compound [C] is an antimicrobial and antiviral agent (e.g., antibiotics, proteins, peptides, peptidomimetics, brilacidin, antibodies, etc.) with brilacidin as an example, wherein the said compound is the same drug attached, adsorbed or chemically conjugated and used in the configuration of the present invention;

[0015] The compound [C] is a different antimicrobial and antiviral drug, attached, adsorbed or chemically conjugated and used in the configuration of the present invention;

[0016] The compound [C] is absent from the configuration of the present invention;

[0017] The compound [D] is hemin, a strong inducer of an endogenous cytoprotective enzyme heme oxygenase-1 (HO-1), wherein the said compound is the same drug attached, adsorbed or chemically conjugated and used in the configuration of the present invention;

[0018] The compound [D] is a different inducer of HO-1, wherein the said compound is a different drug attached, adsorbed or chemically conjugated and used in the configuration of the present invention;

[0019] The compound [D] is inducer of HO-1 via upstream transcription factor Nrf2, including but not limited to, 4-octyl-itaconate and dimethyl fumarate, wherein the compound is adsorbed or chemically conjugated and used in the configuration of the present invention;

[0020] The compound [D] is absent from the configuration of the present invention; The compound [E] is low molecular weight heparin (LMWH), anticoagulants, low- or non-anticoagulant heparin, and other modified glycosaminoglycans (GAG) derivatives, including heparin, wherein the said compound is the same drug attached, adsorbed or chemically conjugated and used in the configuration of the present invention;

[0021] The compound [E] is a different LMWH, anticoagulants, low- or non-anticoagulant heparin, and other modified GAG derivatives, including heparin, wherein the said compound is different drug attached, adsorbed or chemically conjugated and used in the configuration of the present invention;

[0022] The compound [E] is a different compound possessing a net negatively charge attached, adsorbed or chemically conjugated and used in the configuration of the present invention;

[0023] The compound [E] is absent from the configuration of the present invention;

[0024] The “Other drug formulations” [F] is a drug, drug components, or drug combinations exhibiting antiviral, antimicrobial, cytoprotective, anti-inflammatory, and anticoagulant activities used in the configuration of the present invention;

[0025] The “Other drug formulations” [F] is a drug or drug components exhibiting antiviral activity, including but not limited to, remdesivir, favipiravir, polyclonal or monoclonal antibodies, proteins, peptides, peptidomimetics, nucleotides, etc., either individually or in any preferred combinations used in the configuration of the present invention;

[0026] The “Other drug formulations” [F] is a drug, drug components, or drug combinations exhibiting anti-inflammatory activity, including but not limited to, corticosteroids,

indomethacin, other nonsteroidal anti-inflammatory drugs (NSAIDs), etc., used in the configuration of the present invention;

[0027] The compound [F] is absent from the configuration of the present invention.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0028] Respiratory pathogens are known to primarily target the lung (Subbarao, K. & Mahanty, S. *Immunity*. 52:905-909 (2020)). These pathogens enter through the nasal or oral cavity. Therefore, it is desirable to target the nasal cavity, oral cavity, nasopharynx, and posterior pharynx directly where the primary infections occur to provide rapid and robust protection.

[0029] This invention relates to a therapeutic swabs device system comprising plurality of drugs possessing various crucial cellular protective functions (e.g., antiviral, antimicrobial, cytoprotective, and anti-inflammatory) intended to specifically and directly targeting the primary sites of upper respiratory infections. The approach presented in this invention not only has the potential to effectively treat upper respiratory infections, it can also reduce the risk of adverse side effects associated with high systemic absorption of drugs that are administered in the form of oral medicines or injections. The multifactorial generic antiviral therapeutic approach presented in this invention is much-warranted to control the current out-of-control COVID-19 pandemic situation.

[0030] As will be familiar to those skilled in the art, systemic administration of drugs either orally, by injections, or via other routes is not without the risk of causing adverse effects, sometimes serious in nature. The preferred embodiment of the present invention contemplates to Therapeutic Swabs device system as a therapeutic device for delivering plurality of drugs exhibiting distinct antiviral, antimicrobial and cytoprotective functions for specifically targeting the nasal cavity, nasopharynx, and throat, the primary sites of upper respiratory infections.

[0031] It will be appreciated that one or more crucial drugs are delivered simultaneously and directly to the infected sites of upper respiratory infections for maximizing their effectiveness, signifying a broader public health utility of the present invention. Accordingly, an embodiment of the present invention relates to selection of plurality of drugs possessing: (a) antiviral activity to disrupt the viruses or inhibit viral replication; (b) anti-inflammatory activity to reduce inflammation associated with viral infections; (c) cytoprotective function to prevent virus-induced cell death; (d) anticoagulant activity to reduce blood clotting in upper respiratory viral infections; and (e) bearing the net negatively charged moieties on one or more drugs to potentially bind the positively charged viruses and, as a result, protect the target cells from being infected.

[0032] The term “antiviral/antimicrobial drugs” used herein (e.g., antiviral, antimicrobial, antibiotics, proteins, peptides, peptidomimetics, antibodies, nucleotides, etc.), depicted as [C] in FIG. 1 and FIG. 2 of this invention, signifies drugs or compounds, synthetic or natural products, exhibiting antiviral or antimicrobial activity. An embodiment of the present invention relates to utility of brilacidin, a peptide or a biomimetic antimicrobial polymer derived from a host protein defensin exhibiting antiviral and antibacterial activities (Tew et al. *Proc. Natl. Acad. Sci.*

99:5110-5114 (2002); Ding, J., Chou, Y. Y. & Chang, T. L. J. Innate Immunity. 1:413-420 (2009); Som et al. Clin. Vaccine Immunol. 19:1784-1791 (2012); Brice, D. C. & Diamond, G. Curr. Med. Chem. 27:1420-1443 (2020); Di, Y. P. Curr. Med. Chem. 27:1385-1386 (2020); Bakovic et al. Viruses. 13:271, (2021)), depicted as [C] in FIG. 1 and FIG. 2, in the configuration of the present invention. Brilacidin may be substituted with other drugs or agents exhibiting antimicrobial characteristics.

[0033] An embodiment of the present invention specifically utilizes heme oxygenase-1 (HO-1)-inducing drugs, depicted as [D], providing a strong “generic innate cellular protection” against a wide variety of infections, regardless of types, mutants, or strains of the pathogens, such as HIV-1, Ebola virus, Vaccinia virus, Zika virus, West Nile virus, Dengue virus, even a parasite *Leishmania donovani*, and, more recently, a mycoplasma *Mycoplasma hyorhinis* (Devadas, K. & Dhawan, S. J. Immunol. 176:4252-4257 (2006); Zhou et al. Curr. Trends Immunol. 14:53-56 (2013); Dhawan, S. Curr. Trends Immunol. 14:65-70 (2013); Meseda et al. Biochem. Biophys. Res. Commun. 454:84-88 (2014); Huang et al. Curr. Trends Immunol. 17:117-123 (2016); Hill-Batorski et al. J. Virol. 87:13795-13802 (2013); Huang et al. Virology. 503: 1-5 (2017); Chi et al. J. Transl. Med. 14:35 (2016); Wagener et al. Antioxidants. 9:540 (2020); Chi et al. J. Transl. Med. 14:35 (2016); Rossi et al. Med. Hypothesis. 144:110242 (2020); Huang et al. FEBS Open Bio. Published online on Aug. 10, 2021; <https://doi.org/10.1002/2211-5463.13271>; Dhawan, S. Curr. Trends Immunol. 22:19-21 (2021); Dhawan, S. Curr. Trends Immunol. 22:43-47 (2021); Dhawan, S. Am. Pharm. Rev. 48-49 (May/June 2021)). Therefore, the utility of HO-1 inducers in the configuration of this invention presents a significant advancement for the general host protection against infections.

[0034] It will be appreciated that hemin, depicted as [D] in FIG. 1 and FIG. 2 of this invention, is the active component of a previously FDA-approved drug Panhematin® for another indication (Siegert, S. W. & Holt, R. J. Adv. Ther. 9:842-857 (2008); therefore, this highly significant advantage rules out any serious adverse side effects of this drug that induces strong innate cytoprotective, anti-inflammatory, and antiviral functions.

[0035] The term “HO-1 inducer”, including Nrf2-dependent (or independent) HO-1 inducers, depicted as [D] in FIG. 1 and FIG. 2 of this invention, signifies the agents exhibiting potent cytoprotective activity against infections that are much-needed to effectively combating and for inducing a robust innate host defense against deadly infections.

[0036] The drugs depicted as [C] and [D] in FIG. 1 and FIG. 2 of this invention, may be substituted with other drugs or agents exhibiting similar functional characteristics.

[0037] A rare blood clotting in certain COVID-19-vaccinated individuals is reported (Ledford, H. Nature 596:479-481 (2021)). Whereas heparin is thought to be linked to blood clotting (cited in the above reference), non-anticoagulant heparin derivative, the low molecular weight heparin (LMWH), has been reported to elicit beneficial effects on mortality in COVID-19 by: (a) inhibition of heparinase activity; (b) reduction of chemokines and cytokines; (c) interference with leukocyte trafficking; and (d) reducing viral cellular entry (Buijsers et al. EBioMedicine. 59:102969 (2020)).

[0038] Accordingly, an embodiment of the present invention is anticoagulants or low-anticoagulants, e.g., chondroitin sulfate (CS), LMWH, or modified low- or non-anticoagulant glycosaminoglycans (GAG) derivatives, including N-acetylated glycol-split heparin, and other heparin modifications, depicted as [E] in FIG. 1 and FIG. 2, providing a beneficial utility of non-anticoagulant activity or reduced anticoagulant activity in the configuration of the present invention without unwanted side effects (Duckworth et al. Oncotarget. 6:23671-23687 (2015); Casu, B., Vlodaysky, I & Sanderson, R. D. Pathophysiol. Haemost. Thromb. 36:195-203 (2009)).

[0039] CS is a small molecule with molecular mass of ~463 Da as compared to heterogeneous heparin with high molecular mass ranging between 3,000 Da to 30,000 Da. Therefore, CS, LMWH or other modified GAG derivatives present better and useful alternatives for use in the configuration of this invention. In addition, the net negative charge on CS, LMWH or modified GAGs could potentially bind positively charged upper respiratory viruses, including SARS-CoV-2, to prevent their attachment to the target cells.

[0040] The low- or non-anticoagulant heparin, LMWH, or modified GAG derivatives, including heparin, depicted as compound [E] in FIG. 1 and FIG. 2, may be used or replaced by other independent drug molecules possessing net negatively charged moieties.

[0041] The term “Other drug formulations” (shown as [F] in FIG. 1 and FIG. 2) used herein refers to drugs or drug components exhibiting antiviral, antimicrobial, anti-inflammatory, anticoagulant, cytoprotective, and other relevant crucial medicinal functions.

[0042] Therapeutic Swabs device system presents a significant advantage over conventional administration of antiviral and antimicrobial drugs for treating upper respiratory infections via other routes (e.g., pills, capsules, via injections, etc.) in terms of minimizing high systemic absorption of the drugs. This invention also presents much superiority over the antiviral and antimicrobial drug administration by nasal drops or nasal sprays in terms of minimizing the dripping or spilling of the drugs and/or contaminated nasal secretions. Collectively, this invention presents a novel configuration designed for an effective therapeutic approach for targeting specifically the infected sites of upper respiratory infections enabling a broadly applicable remedy for treating upper respiratory infections in the humans and in animals.

[0043] The utility of the present invention will have a tremendous positive impact on the public health safety on a mass-scale in controlling the current COVID-19 pandemic crisis as well as in preparing us for the unforeseen future viral outbreaks. The Therapeutic Swabs device system presents a convenient and useful therapeutic tool to offer medical intervention by healthcare professionals, by other individuals, by friends and family members, by self-administration, and for home use to minimize the spread of deadly respiratory infections to others and to retard the disease progression.

1-3. (canceled)

4. A therapeutic swab device consisting of:

a stem having a first end and a second end;

a first drug-loaded swab located at the first end, the first drug-loaded swab consisting of a swab and a first plurality of drugs consisting of a first composition consisting of:

at least one antiviral agent,
 at least one heme oxygenase-1 (HO-1) inducer selected from the group consisting of hemin, 4-octyl-itaconate, dimethyl fumarate, and combinations thereof,
 an anticoagulant selected from a modified heparin, a low molecular weight heparin (LMWH), chondroitin sulfate (CS), and a modified glycosaminoglycans (GAG), and
 a drug component having anti-inflammatory activity; and
 a second drug-loaded swab located at the second end, wherein the second drug-loaded swab consists of a second plurality of drugs identical to the first composition,
 wherein the therapeutic swab is configured for use in a nasopharynx and a posterior pharynx of a subject.
 5. (canceled)
 6. (canceled)
 7. The therapeutic swab of claim 4, wherein the stem is rigid.
 8. The therapeutic swab of claim 4, wherein the stem is flexible.
 9. The therapeutic swab of claim 4, wherein the antiviral agent is a protein.
 10. The therapeutic swab of claim 4, wherein the antiviral agent is a peptide.
 11. The therapeutic swab of claim 4, wherein the antiviral agent is a peptidomimetic.
 12. The therapeutic swab of claim 4, wherein the antiviral agent is an antibody.
 13. The therapeutic swab of claim 4, wherein the anticoagulant is a modified heparin.
 14. The therapeutic swab of claim 4, wherein the anticoagulant is LMWH.
 15. The therapeutic swab of claim 4, wherein the anticoagulant is CS.
 16. The therapeutic swab of claim 4, wherein the anticoagulant is GAG.
 17. A therapeutic swab device for treating an upper respiratory infection in a subject, the therapeutic swab comprising:
 a stem having a first end and a second end;
 a first drug-loaded swab located at the first end, the first drug-loaded swab consisting of a swab and a first plurality of drugs consisting of:
 brilacidin,
 at least one innate heme oxygenase-1 (HO-1) inducing agent selected from hemin, 4-octyl-itaconate, dimethyl fumarate, and combinations thereof,

at least one anticoagulant selected from a modified heparin, a low molecular weight heparin (LMWH), chondroitin sulfate (CS), and a modified glycosaminoglycans (GAG), and
 at least one drug component having anti-inflammatory activity,
 wherein the therapeutic swab is configured for use in a nasopharynx and a posterior pharynx of a subject.
 18. The therapeutic swab of claim 17 further comprising a second drug-loaded swab located at the second end.
 19. The therapeutic swab of claim 18, wherein the second drug-loaded swab includes a second plurality of drugs having a composition identical to the first plurality of drugs.
 20. (canceled)
 21. The therapeutic swab of claim 17, wherein the stem is rigid.
 22. The therapeutic swab of claim 17, wherein the stem is flexible.
 23. A method of treating an upper respiratory infection in a human subject, the method comprising:
 locally administering a plurality of drugs located on a drug-loaded swab to at least one body region of the subject,
 the at least one body region including the posterior pharynx of the human subject, and
 the plurality of drugs consisting of:
 at least one antiviral agent,
 hemin,
 an anticoagulant selected from a modified heparin, a low molecular weight heparin (LMWH), chondroitin sulfate (CS), and a modified glycosaminoglycans (GAG), and
 a drug component having anti-inflammatory activity.
 24. The method of claim 23, further comprising locally administering the plurality of drugs located on both ends of a double-ended drug-loaded swab to the nasal cavities, oral cavities, and nasopharynx of a subject.
 25. The method of claim 23, further comprising locally administering the plurality of drugs located on both ends of a double-ended drug-loaded swab to the nasal cavities, oral cavities, or nasopharynx of the subject.
 26. The therapeutic swab of claim 4, wherein the heme oxygenase-1 (HO-1) inducer is hemin, 4-octyl-itaconate, or dimethyl fumarate.
 27. The therapeutic swab of claim 4, wherein the heme oxygenase-1 (HO-1) inducer is dimethyl fumarate.
 28. The therapeutic swab of claim 4, wherein the heme oxygenase-1 (HO-1) inducer is 4-octyl-itaconate.
 29. The therapeutic swab of claim 4, wherein the heme oxygenase-1 (HO-1) inducer is hemin.

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